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TOTAL SYNTHESIS OF (±)-AVENACIOLIDE AND ITS ANALOGUES

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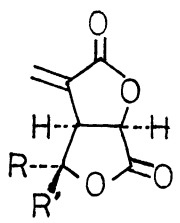
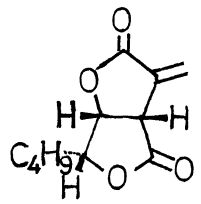
A new method for the stereoselective synthesis of (±)-avenaciolide and its analogues via methoxycarbonyl- or anisyloxycarbonyldi-γ-lactones, which could be easily prepared by the reaction of γ-substituted α-bromobutenolides with sodium salt of methyl or anisyl malonamate in good yields, was described.

Among a variety of biological active natural products, the compounds which contain one or two α-methylene-γ- or δ-lactone functional units have received considerable attention in recent years owing to their various kinds of biological activities e. g., antibacterial, antimold, antitumor or plant growth inhibitory properties.[1] In these a series of compounds, which possess a unique di-γ-lactone structure, such as avenaciolide,[2,3] isoavenaciolide,[4] ethisolide [4a] and canadensolide,[5] were isolated from microorganisms. Avenaciolide (1a) is a mold metabolite produced by Asperigillus avenaceus[2] and A. fischeri var. glaber[3] and has an antigerminate activity against fungi.[2] In our previous paper[6] we reported a convenient method for the stereoselective preparation of methoxycarbonyldi-γ-lactone (9), a key intermediate of methylenedi-γ-lactone (1), by the reaction of α-bromobutenolide (5) with sodium salt of methyl malonamate (6). This paper describes a stereoselective total synthesis of (±)-avenaciolide (1a) and its 4-ethyl (1b) and 4-methyl (1c) analogues.

α-Bromobutenolide (5a) was prepared in 85% yield by the reaction of the butenolide (4a) with equimolar amount of bromine in carbon tetrachloride at room temperature for 15 h, followed by the treatment of the crude dibromide with 2 molar amounts of triethylamine in benzene at 0°C for 3h. In a similar manner,



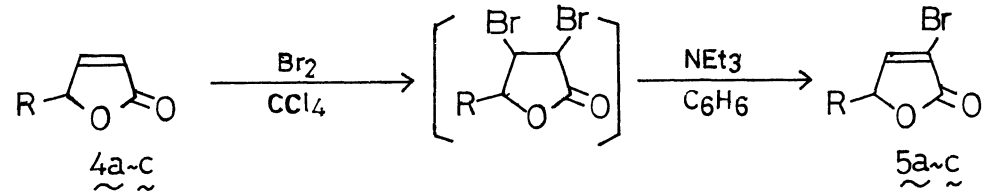
1a R=C_8H_{17} R'=H avenaciolide
b R=C_2H_5 R'=H
c R=CH_3 R'=H
2a R=H R'=C_8H_{17} isoavenaciolide
b R=H R'=C_2H_5 ethisolide



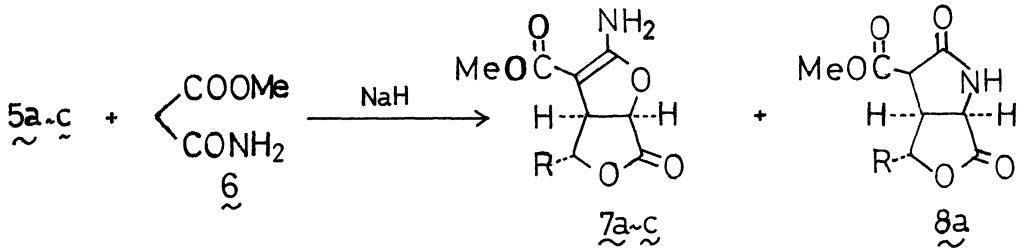
3 canadensolide

5b and 5c were prepared in 68 and 54% yields, respectively. The reaction of 5a with sodium salt of methyl malonamate (6) in a co-solvent of THF and HMPA at 0°C for 2 h afforded aminodihydrofuran derivative (7a) in 62% yield along with lactam derivative (8a, 8% yield).[6] Both were characterized by ^{1}H NMR and IR spectral data and elemental analysis.[9] When 7a was treated with 1.2 molar amount of 0.1 M HCl at room temperature for 3 h, the desired methoxycarbonyldilactone (9a) was obtained quantitatively. Similarly from 5b and 5c, the corresponding dilactone (9b and 9c) were prepared in 40 and 36% yields, respectively.

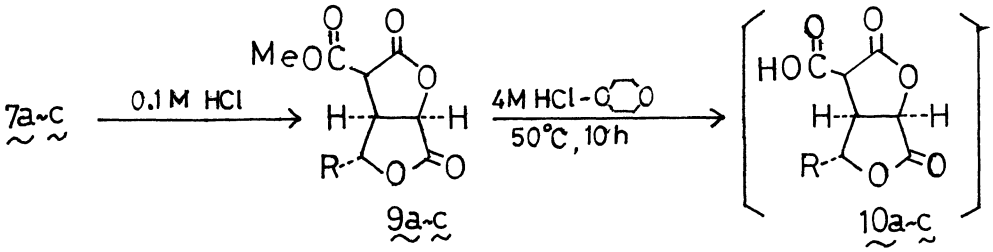
The hydrolysis of methoxycarbonyl group of 9a to carboxylic acid (10a) was performed by the treatment with 4 M HCl-dioxane at 50°C for 10 h, though the hydrolysis was not completed and the formation of a small amounts of unidentified by-products was observed. The longer reaction time or the more drastic reaction conditions resulted in the formation of a large amounts of by-products. Under the milder reaction conditions, the hydrolysis proceeded only very slowly. The resulted crude acid (10a) was successfully converted into (±)-avenaciolide (1a) by the procedure of Parker and Johnson[7a] in 34% yield from 9a. The melting point coincided with the reported value of synthetic (±)-avenaciolide.[10] The ^{1}H NMR



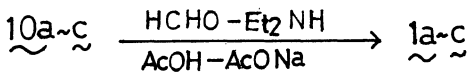
4a~c 5a~c



5a~c + 6 → 7a~c + 8a



7a~c → 9a~c → 10a~c

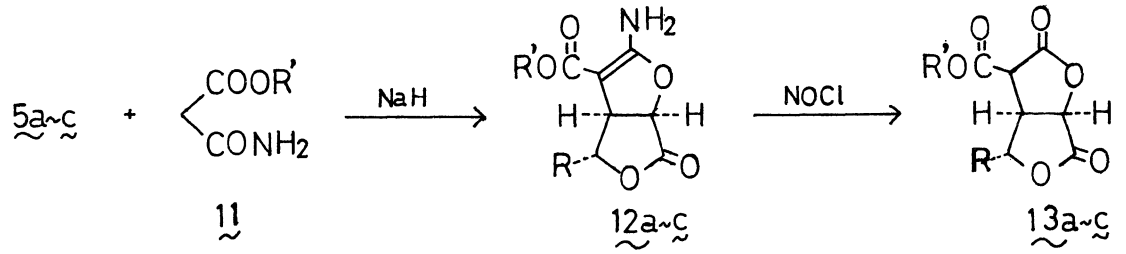


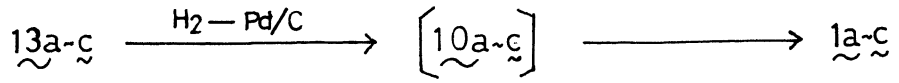
10a~c → 1a~c

a R = C_8H_{17}
b R = C_2H_5
c R = CH_3

data of 1a were in fair agreement with those of natural avenaciolide[2] and were different from those of isoavenaciolide (2a).[4a] We could not recognize the formation of any trace of isoavenaciolide nor its intermediate, an epimer of aminodihydrofuran (7a). These indicate that the addition reaction of sodium salt of methyl malonamate (6) to the butenolide (5a) proceeds stereoselectively and the stereochemical relationship between the alkyl substituent and the introduced lactone ring is trans. Therefore, it can be said that the nucleophile attacks only from the less hindered side of the butenolide. Similarly, ethyl analogue (1b), which can be regarded as an epimer of ethisolide (2b), and methyl analogue (1c) of avenaciolide were synthesized from dilactone esters (9b and 9c) in 54 and 46% yields, respectively.[10]

The present method provides short step synthesis of (±)-avenaciolide and its analogues though some difficulty lies in hydrolysis step, 9 to 10. However, this difficulty could be overcome by the use of anisyl malonamate (11) instead of 6 as a starting material. The anisyl ester (11) also reacted with 5 in THF-HMPA at 0°C to afford aminodihydrofurans, (12a) in 64% yield, (12b) in 73% yield and (12c) in 60% yield. The yields were higher than those of the corresponding methyl esters (7). The hydrolysis of 12a to dilactone ester (13a) was best performed, different from that of 7a, by introducing NOCl gas slowly into the ether solution of 12a at room temperature (70% yield). Removal of the anisyl group from dilactone ester (13a) to the carboxylic acid derivative (10a) was achieved by hydrogenolysis with 20% palladium-carbon in methanol under atmospheric pressure of hydrogen at a room temperature. By the procedure, the acid (10a) was obtained in nearly quantitative yield in almost pure state. The acid was then converted into (±)-avenaciolide (1a) in 60% yield from 13a by the method of Parker and Johnson.[7a] Consequently the overall yield was improved.





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8) Synthesis of optically active avenaciolide: a) R. C. Anderson and B. Fraser-Reid, J. Am. Chem. Soc., 97, 3879 (1975); b) H. Ohrui and S. Emoto, Tetrahedron Lett., 1975, 3657.

9) Satisfactory elemental analyses were obtained on the intermediates, 7, 8, 9, and 12. All of the isolated intermediates gave IR and NMR spectral data in accord with their assigned structures.

10) 1a: Mp 55.0-55.5°C (lit. mp 55-56°C[7a,b]); IR(KBr) 1790 (C=O) and 1660 cm^{-1} (C=C); NMR($CDCl_3$) δ=0.90 (3H, t), 1.20-1.80 (14H), 3.57 (1H, m), 4.33 (1H, m), 4,98 (1H, d, J=9Hz), 5.80 (1H, d, J=2Hz), and 6.32 (1H, d, J=2Hz); Found: C, 67.92; H, 8.44%. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33%.
1b: Mp 64-65°C; IR(KBr) 1780 (C=O) and 1670 cm^{-1} (C=C); NMR($CDCl_3$) δ=1.07 (3H, t), 1.90 (2H, m), 3.60 (1H, m), 4.40 (1H, m) 5.10 (1H, d, J=9Hz), 5.93 (1H, d, J=2Hz), and 6.50 (1H, d, 2Hz); Found: C, 59.40; H, 5,49%. Calcd for $C_9H_{10}O_4$: C, 59.33; H, 5.49%.
1c: Mp 113-114°C; IR(KBr) 1780 (C=O) and 1670 cm^{-1} (C=C); NMR($CDCl_3$) δ=1.60 (3H, d, 6Hz), 3.63 (1H, m) 4.63 (1H, m) 5.17 (1H, d, 8Hz), 5.97 (1H, d, 2Hz) and 6.53 (1H, d, 2Hz); Found: C, 57.01; H, 4.82%. Calcd for $C_8H_8O_4$: C, 57.14; H, 4.80%.

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